themselves, and finally to synthesise a basement membrane around the new vessels.

Angiogenesis is prominent in the growth and remodeling of tissues, including wound healing and inflammatory processes. Tumors must initiate angiogenesis when they reach millimeter size in order to keep up their rate of growth. Angiogenesis is accompanied by characteristic changes in endothelial cells and their environment. The surface of these cells is remodelled in preparation for migration, and cryptic structures are exposed where the basement membrane is degraded, in addition to the variety of proteins which are involved in effecting and controlling proteolysis. In the case of tumors, the resulting network of blood vessels is usually disorganised, with the formation of sharp kinks and also arteriovenous shunts. Inhibition of angiogenesis is also considered to be a promising strategy for antitumor therapy. The transformations accompanying angiogenesis are also very promising for diagnosis, an obvious example being malignant disease, but the concept also shows great promise in inflammation and a variety of inflammation-related diseases, including atherosclerosis, the macrophages of early atherosclerotic lesions being potential sources of angiogenic factors. These factors are also involved in re-vascularisation of infarcted parts of the myocardium, which occurs if a stenosis is released within a short time.

Further examples of undesired conditions that are associated with neovascularization or angiogenesis, the development or proliferation of new blood vessels are listed in Table 1 below. Reference is also made in this regard to WO98/47541.

Diseases and indications associated with angiogenesis are e.g. different forms of cancer and metastasis, e.g. breast, skin, colorectal, pancreatic, prostate, lung or ovarian cancer.

Other diseases and indications are inflammation (e.g. chronic), atherosclerosis, rheumatoid arthritis and gingivitis.

Further diseases and indications associated with angiogenesis are arteriovenous alformations, astrocytomas, choriocarcinomas, glioblastomas, gliomas, hemangiomas (childhood, capillary), hepatomas, hyperplastic endometrium, ischemic myocardium, Kaposi sarcoma, macular degeneration, melanoma, neuroblastomas, occluding peripheral artery disease, osteoarthritis, psoriasis, retinopathy (diabetic, proliferative), scleroderma, seminomas, solid tumor formation and ulcerative colitis.

Angiogenesis involves receptors which are unique to endothelial cells. The integrin $\alpha v\beta 3$ is one of the receptors that is known to be associated with angiogenesis. Stimulated endothelial cells appear to rely on this receptor for survival during a critical period of the angiogeneic process, as antagonists of the $\alpha v\beta 3$ integrin receptor/ligand interaction induce apoptosis and inhibit blood vessel growth.

The integrin $\alpha v\beta 3$ is a member of a family of transmembrane proteins that act as receptors through which cells can adhere to the extracellular matrix. Integrins are heterodimeric molecules in which the α- and β-subunits penetrate the cell-membrane lipid bilayer. The α-subunit has four Ca^{2+} binding domains on its extracellular chain, and the β-subunit has a number of extracellular cysteine-rich domains.

Many ligands (eg. fibronectin) involved in cell adhesion contain the tripeptide sequence arginine-glycine-aspartic acid (RGD). The RGD sequence appears to act as a primary recognition site between the ligands presenting this sequence and receptors on the surface of cells. It is generally believed that secondary interactions between the ligand and receptor enhance the specificity of the interaction. These secondary interactions might take place between moieties of the ligand and receptor that are immediately adjacent to the RGD sequence or at sites that are distant from the RGD sequence.

RGD peptides are known to bind to a range of integrin receptors and have the potential to regulate a number of cellular events of significant application in the clinical setting. (Ruoslahti, *J. Clin.* Invest., 87: 1-5 (1991)). Perhaps the most widely studied effect of RGD peptides and mimetics thereof relate to their use as anti-thrombotic agents where they target the platelet integrin GpIIbIIIa.

Inhibition of angiogenesis in tissues by administration of either an $\alpha v\beta 3$ or $\alpha v\beta 5$ antagonist has been described in for example WO 97/06791 and WO95/25543 using either antibodies or RGD containing peptides. EP 578083 describes a series of mono-cyclic RGD containing peptides and WO 90/14103 describes RGD-antibodies. Haubner et al. in the *J. Nucl. Med.* (1999); 40: 1061-1071 describe a new class of tracer for tumour targeting based on monocyclic RGD containing peptides. Biodistribution studies using whole-body autoradiographic imaging revealed however that the ^{125}I-labelled peptides had very fast blood clearance rates and predominantly hepatobiliary excretion routes resulting in high background noise.